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What covid-19 does to the brain

The latest evidence suggests neurological symptoms of long covid, such as brain fog, are caused by an immune reaction – and should be reversible, reports **Jessica Hamzelou**

OVER the past two years, we have learned that covid-19 can have profound consequences for the brain – in the short and long term.

Now, researchers are starting to get a clearer picture of how the coronavirus may cause symptoms that include brain fog, depression, confusion and even stroke. The latest insights suggest that the virus seldom infects brain cells directly, but instead causes harm through blood clots or by spurring a destructive immune response. Encouragingly, many of the effects caused by harmful immune changes are likely to be reversible.

It is estimated that, in the early stages of infection, roughly 1 in 4 people experience depression. Longer term, the neurological and mental health toll may be even higher. An analysis of medical records from some 230,000 people based mainly in the US who recovered from covid-19 found that a third went on to be diagnosed with a neurological or psychiatric condition within six months. In a survey of nearly 1000 people in the US with long-term symptoms, 47 per cent reported brain fog, difficulty concentrating or forgetfulness.

It isn't uncommon for the brain to be affected after a viral infection; this has been seen with Zika, polio, measles and flu. But rates of lingering neurological or mental health problems appear to be higher after covid-19 than after many other viral infections.

Some neuroscientists have hypothesised that the coronavirus causes such symptoms by directly attacking cells in the brain, as HIV and the virus that causes herpes are able to do. But the emerging picture from autopsy studies

of brain tissue is that while the coronavirus can get into the brain, it doesn't appear to replicate there or damage brain tissue directly, says Serena Spudich at Yale University. She has summarised some of the latest findings alongside Avindra Nath at the US National Institute of Neurological Disorders and Stroke in a paper in *Science* (doi.org/gn7nss).

The effects on the brain may largely be down to two other important factors. One is the impact of covid-19 on blood vessels. Multiple studies have found abnormal clotting, which

"Rates of neurological problems appear to be higher after covid-19 than after other viral infections"

can cause stroke, in people with severe cases of covid-19. Autopsies have also revealed damage to blood vessels in the brain after covid-19 – vessel walls have become thinner, and they appear to leak proteins that might trigger an immune response.

This altered immune response

has come to the fore as potentially the most significant culprit. In autopsy studies of people who had covid-19, researchers seldom see virus in samples of cerebrospinal fluid (CSF), the liquid that bathes the brain and spinal cord. Other studies of CSF from people with covid-19 have found changes in immune cells, including a higher production of chemicals that can be toxic to brain cells.

To try to understand the mechanisms driving these immune responses, Michelle Monje at Stanford University in California and her colleagues looked to parallels between the brain fog symptoms of long covid and "chemo brain", the thinking and memory problems that can follow chemotherapy.

Those symptoms seem to be caused by the body's immune response to the chemotherapy. The microglia, immune cells of the central nervous system, enter a more inflammatory state and change how other brain cells behave: less protective myelin is laid down on neurons, fewer neurons are generated and

other brain cells are destroyed.

To find out whether something similar is happening in people with long covid, Monje and her colleagues studied mice that can be infected with the coronavirus, but only in their airways as they lack the receptor for direct infection in the brain.

Stark parallels

Monje's team found chemicals in the animals' blood and CSF that indicate they are experiencing something very similar to mouse models of chemo brain. Their brains also showed the same change in microglia cells, and a reduction in the generation of new brain cells. "We found really stark parallels," says Monje.

In that work, which hasn't yet undergone peer review, the team also looked at brain tissue from nine people who had died from or with covid-19. In all nine people, the changes in microglia in the white matter were similar to what they saw in the mouse brains ([bioRxiv, doi.org/gn4fcp](https://doi.org/gn4fcp)).

In samples from the mice, the group also found the immune substance CCL11, which has been linked to problems with cognition. In another experiment, Monje and her team looked at CCL11 levels in blood samples from people with long covid and found they were higher in those with cognitive symptoms than in those without.

Together, these findings strengthen the idea that immune responses are behind some of the effects of covid-19 on the brain. While severe impacts like stroke can cause lasting damage, "nothing that we showed in this paper should be irreversible," says Monje.

She thinks that treatments could be developed that take the brain back to a healthy state. "It's a message of hope," she says. ■



Scans of a person's brain are viewed by a doctor